Modelling the economic impact of recombinant activated Factor VII compared to activated prothrombin-complex concentrate in the home treatment of a mild to moderate bleed in adults with inhibitors to clotting Factors VIII and IX in the UK

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of recombinant activated Factor VII (rFVIIa; NovoSeven) and activated prothrombin-complex concentrate (aPCC; FEOBA), both administered at home, to treat a minor (mild to moderate) bleeding episode in patients with haemophilia A or B.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised adult patients suffering from haemophilia A or B with high titre and high responding inhibitors (greater than 10 BU).

Setting
The setting was the patient's home. The economic study was conducted in the UK.

Dates to which data relate
The effectiveness data were derived from two studies published in 1990 and 1998. The dates for the resource use data were not provided. The prices related to 1999/2000.

Source of effectiveness data
The effectiveness evidence was derived from a review of completed studies and from experts' opinions.

Modelling
A modelling approach, based on a decision tree, was used to assess the costs and consequences of aPCC versus rFVIIa for treating minor bleeds. The time horizon of the model was not reported. The tree comprised:

- the initial home treatment;
- subsequent treatments for a bleed at the Comprehensive Care Centre (CCC);
- the probability of switching from one treatment to another;
the duration of each treatment;

the probability that each treatment would resolve a bleed; and

the probability of a re-bleed and treatment for managing a re-bleed.

The structure of the tree was based on treatment patterns defined by a panel of 22 consultant haematologists from across the UK.

**Outcomes assessed in the review**
The outcome measures assessed in the review were the proportions of bleeds that would either resolve with first-line home treatment or require subsequent treatment at a CCC.

**Study designs and other criteria for inclusion in the review**
The studies included in the review were clinical trials. No other information was given.

**Sources searched to identify primary studies**
Not stated.

**Criteria used to ensure the validity of primary studies**
The studies were selected because they were sufficiently informative to permit comparisons of the number of doses, dosage and efficacy of the treatments.

**Methods used to judge relevance and validity, and for extracting data**
Not stated.

**Number of primary studies included**
Two primary studies were included in the review.

**Methods of combining primary studies**
The primary estimates were not combined as each study was used as a source of evidence for each treatment.

**Investigation of differences between primary studies**
Not stated.

**Results of the review**
The proportion of bleeds that would resolve with first-line home treatment was 79% with aPCC and 92% with rFVIIa.

The proportion of bleeds that would require subsequent treatment at a CCC was 21% with aPCC and 8% with rFVIIa.

**Methods used to derive estimates of effectiveness**
A Delphi panel, including seven haematologists, was used to estimate the probabilities of stopping or continuing bleeding after treatment in a CCC with aPCC or rFVIIa.
Estimates of effectiveness and key assumptions
For patients treated at home with aPCC who continued bleeding, the probability that bleeds would resolve was:

- 65% after again receiving aPCC at a CCC as day cases,
- 87% after again receiving aPCC at a CCC as an inpatient,
- 85% after receiving rFVIIa at a CCC as a day case, and
- 100% after receiving porcine Factor VII at a CCC as an inpatient.

For patients treated at home with rFVIIa who continued bleeding, the probability that bleeds would resolve was 65% after again receiving rFVIIa at CCC as day cases, and 90% after receiving rFVIIa at a CCC as an inpatient.

All patients who did not resolve bleeding after being treated once at a CCC with both therapies were assumed to again receive rFVIIa, with a 100% probability that bleeding would stop.

Measure of benefits used in the economic analysis
The model output was the expected time to resolve a minor bleed at home. This was derived from the decision model. No discounting was applied.

Direct costs
Discounting was not relevant since the costs were incurred during a short time. The unit costs were not presented separately from the quantities of resources used. However, resource use associated with medication, and days in a CCC were reported. The health services included in the economic evaluation were study drugs, concomitant medications, outpatient visits, inpatient stay, clinical test or investigations, and ambulance transport. The cost/resource boundary of the NHS was adopted. Resource use was estimated using information obtained from the expert panel using a Delphi process. All the assumptions about patient management, treatment paths and resource use were reported. The costs were estimated from the Personnel Social Services Research Unit, the Monthly Index of Medical Specialties, and Drug Tariff from the Department of Health. The costs were estimated in 1999/2000 values.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not considered.

Currency
UK pounds sterling (€).

Sensitivity analysis
A threshold analysis was conducted to assess the robustness of the cost results to variations in all the probability and resource use data entered into the decision model. Wide ranges of values were used to reflect the uncertainty. The sources for the ranges used were not reported.

Estimated benefits used in the economic analysis
The expected time to resolve a minor bleed at home was 32 hours with rFVIIa and 60 hours with aPCC.

The probability of bleeds being resolved within 48 hours was 78% with rFVIIa and 66% with aPCC. The probability of
bleeds being resolved within 96 hours was 21% with rFVIIa and 17% with aPCC.

Cost results
The expected costs were 12,944 with rFVIIa and 14,645 with aPCC.

The estimated costs were sensitive to the number of doses and dosages of the study drugs, the probability of successful treatment at home, and the time to a bleed being resolved at home following initial treatment with either study drug. However, the authors noted that the relative economic impact of rFVIIa was not sensitive to the number of doses and dosage of any drugs administered second-line or later, or any other component of treatment.

The probability that the expected cost per bleeding episode was below 10,000 was 77% with rFVIIa and 68% with aPCC.

Synthesis of costs and benefits
The costs and benefits were not combined because rFVIIa was both more effective and less costly than aPCC (rFVIIa dominant strategy).

Authors' conclusions
The use of recombinant activated Factor VII (rFVIIa) at home instead of activated prothrombin-complex concentrate (aPCC) approximately halved the time to resolving a minor bleeding episode while being, at the least, cost neutral.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was clear. The authors stated that aPCC and rFVIIa are commonly used in patients with high titre and high responding inhibitors (greater than 10 BU), who do not respond to conventional therapies. However, since the NHS had not advised on implementing UK guidelines, there was no consensus on the role of the different products. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
The analysis of effectiveness used data derived from two studies identified in a literature review, the details of which were not reported. The two studies included in the analysis where clinical trials. These were selected because the description of the study protocol and the results were sufficiently informative to allow the two treatment strategies to be compared. However, little information on these studies was given. Therefore, it was difficult to assess the validity of the efficacy measures. However, the authors carried out extensive sensitivity analyses to address the issue of uncertainty surrounding the primary estimates. Experts’ opinions were also used to populate the decision model (probabilities of events) since there was a lack of published studies.

Validity of estimate of measure of benefit
The summary benefit measure was obtained from a decision model that appears to have been appropriate for describing disease progression. However, the summary measure was specific to the interventions considered in the study and is not comparable with the benefits of other health care interventions.

Validity of estimate of costs
The authors explicitly stated the perspective adopted in the study. It appears that all the relevant categories of costs have been included in the analysis. The unit costs and the quantities of resources used were not provided separately, which limits the possibility of replicating the study in other settings. The source of the cost data was reported, as was the price year, which will facilitate reflation exercises. The authors acknowledged that the main limitation of the cost analysis was the use of assumptions made by an expert panel. Nevertheless, these assumptions were essential given the lack of published data on resource use. The authors investigated uncertainty in the sensitivity analysis. Although the estimated
costs were sensitive to several model inputs, the overall cost-neutrality of the two interventions did not change to any great extent.

**Other issues**
The authors compared their results with those from other economic evaluations, especially in terms of costs, and found that, although few studies had been published, similar results were observed. In relation to the generalisability of the study results to other settings, the authors noted that there was some variability in data across the country due to the lack of consensus on the best approach to use. Although information on the unit costs was not given, extensive sensitivity analyses were conducted. These enhance the external validity of the analysis. The authors acknowledged some limitations of the study, mainly the use of experts' assumptions and the sensitivity of the results to some model inputs. The authors stressed that, owing to the low number of inhibitor patients in the UK, the lack of a well-accepted treatment protocol increased the uncertainty in most estimates.

**Implications of the study**
The study results suggested that rFVIIa resolves bleeds in approximately half the time of that with aPCC. Consequently, rFVIIa has the potential to reduce morbidity and hospitalisations in the long term. The results of the current study should be used to inform treatment guidelines and decisions on resource use allocation within the NHS. The authors suggested that future studies should examine the economic and clinical impact of rFVIIa versus aPCC in minimising damage to affected joints or tissues in the longer term.

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**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by CRD

**MeSH**
Blood Coagulation Factors /adverse effects; Cost-Benefit Analysis; Factor VII /adverse effects /therapeutic use; Fatal Outcome; Hemophilia A /drug therapy; Hemophilia B /drug therapy; Recombinant Proteins /adverse effects /therapeutic use; Thrombosis /etiology

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